REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 1 and 10 have been amended to delete the term "optionally", and to recite that X stands for a functional group or moiety capable of binding directly to a biosensor chip surface; that L stands for a linker group or moiety linked to PCL; that L is different from W^1 and W^2; that W^2, PEG, W^1 and L in $(X–W^2–PEG–W^1–L)_x$ and $(L–W^1–PEG–W^2–Y)_y$ are same or different; and that x and y are integers of 1 or more independently of each other, in response to the Examiner's rejections of the claims under 35 U.S.C. § 112, second paragraph. Support for these amendments is found page 10, line 23 through page 11, line 1; page 9, lines 18-23; page 11, lines 14-18; page 5, line 12; and Examples 1 and 3 beginning on pages 23 and 29, respectively of Applicants' specification.

The claims have also been amended to make minor changes of an editorial nature, in order to place to claims in more conventional U.S. format.

Therefore, no new matter has been added to the application.

Rejections under 35 U.S.C. § 112, second paragraph

The rejection of claims 1-15 as being indefinite under 35 U.S.C. § 112, second paragraph is respectfully traversed.

Item 6

The Examiner states that claims 1 and 10 recite the terms "free electron metal fine particle", "metal oxide fine particle" and "semiconductor fine particle". The Examiner asserts that it is not clear what "metals" and "semiconductors" are encompassed in these terms. Further, the Examiner states that the specification does not provide a standard for ascertaining the requisite degree.

However, Applicants' specification recites "PCL can be fine particles of a material selected from a group consisting of free electron materials (e.g., gold, silver, platinum, aluminum, copper and the like), semiconductors (e.g., CdS, ZnS, CdSe, InAs and the like) and metal oxides (e.g., TiO_4, Cr_2O_3 and the like." (See page 9, lines 12-15

of Applicants' specification.) MPEP 2173.02 states that definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the specification, the teachings of the prior art and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Therefore, in view of the teachings in Applicants' specification, as well as the passage from the MPEP, Applicants respectfully assert that the terms "metals" and "semiconductors" are clear, and the portion of the rejection regarding these terms is improper and should be withdrawn.

The Examiner further asserts that the term "fine particle" is a relative term which renders the claim indefinite. Again, the Examiner asserts that the specification does not provide a standard for ascertaining the requisite degree.

However, Applicants' specification recites "PCL can be fine particles of a material.... Those particles having an average cross-sectional size ranging 1-500 nm can be conveniently utilized..." (See page 9, lines 12-17 of Applicants' specification.) Therefore, in view of the teachings in Applicants' specification, as well as the above-discussed passage from the MPEP, Applicants respectfully assert that the term "fine particles" is clear, and the portion of the rejection regarding this term is improper and should be withdrawn.

Item 7

The Examiner states that the term "optionally protected functional groups" in claims 1 and 9 renders the claims indefinite because the term "optionally" is not a positive recitation and may be interpreted as the protected functional group not being a required component of the claimed invention. [Applicants note that claim 9 does not include this term. Applicants assume the Examiner intended to reject claims 1 and 10.] This portion of the rejection is rendered moot by the cancellation of the term "optionally".

Item 8

The Examiner states that claim 1 recites the phrase "Y stands for .... functional moiety X, and functional moieties same as, or different from, X." The Examiner asserts that the function of the "Y group or moiety" in the claim is not clear.

This portion of the rejection is rendered moot by the amendments to claims 1 and 10, which define Y as "at least one group or moiety which is selected from the group consisting of C_1-C_6 alkyl, a group or moiety defined above as X, and a group or moiety defined above as X which is protected, wherein X and Y are not the same simultaneously".

Furthermore, the Examiner inquires when both X and Y are the same functional moiety, do they perform the same function. This question is no longer relevant, due to the claim amendments, which recite that X and Y cannot be the same simultaneously.

The Examiner further states that claim 1 recites that "L", "W^1" and "W^2" can be a linker. The Examiner questions whether the linkers encompassed by "L" are the same as or different from the linkers encompassed by "W^1" and "W^2". This portion of the rejection is rendered moot by the amendments to claims 1 and 10, which recite "wherein L is different from W^1 and W^2".

Item 9

The Examiner states that the phrase "same as" is a relative term and does not establish any metes and bounds to distinguish this term from another. This portion of the rejection has been rendered moot by the amendments to the claims, as discussed above with regard to Item 8.

Item 10

The Examiner states it is unclear what is meant by the term "linkage portion" in claims 1 and 10. This portion of the rejection has been rendered moot by the amendments to claims 1 and 10, which recite "L stands for a linker group or moiety linked to PCL".

Item 11

The Examiner states that claim 1 recites the phrase "X stands for a functional group or a functional moiety capable of binding to biosensor chip surface". The Examiner asserts that it is not clear whether the nanoparticle directly binds to biosensor chip surface through the X functional group or the nanoparticle is first bound to a binding partner/ pair through X functional group before being able to bind to biosensor chip surface.

Applicants' specification recites "X represents a functional group or functional moiety which... may be selected from those expressed by the above formulae (i), (ii) and (iii) which are given as examples of L, or they may be residues of one of the constituents forming aforesaid biological specific binding pair...". (See page 10, lines 13-18 of Applicants' specification.) Thus, "X" may be a functional moiety expressed by formula (i) as well as residues of one of the constituents forming aforesaid biological pair.

On the other hand, biosensor chip surface can be not only "gold" per se, but also a surface which carries "a member capable of forming a biological specific binding pair with the member X...". (See page 13, lines 25-31 of Applicants' specification.) For instance, Example 3 beginning on page 29 of Applicants' specification shows a direct bonding of fine particles with biosensor chip where the functional group of X is amino group, the biosensor chip surface is gold and Y is a member of biological specific binding pair. Example 1 beginning on page 23 of Applicants' specification shows a direct bonding of fine particles with biosensor chip surface caused by the formation of biological specific binding pair.

Therefore, it is clear that the nanoparticles directly bind to biosensor chip surface through the "X" functional group. Applicants have amended claims 1 and 10 to clarify this, and thus have rendered moot this portion of the rejection.

Item 12

The Examiner states that claims 1 and 10 recite the term "may be same or different". The Examiner asserts that the term "may be" is not a positive recitation and therefore renders the claim indefinite. This portion of the rejection has been rendered moot by the replacement of the term "may be" with --are-- in claims 1 and 10.

The Examiner has also asserted that it is unclear what is different when W^2-PEG-W^1-L is "different". This portion of the rejection has been rendered moot by the amendment to claims 1 and 10, which now recite "W^2, PEG, W^1 and L are same or different". It is now clear that each of W^2, PEG, W^1 and L are the same or different from one another.

Item 13

The Examiner states that the term "integers not less than 1" in claim 1 is a relative term. This portion of the rejection has been rendered moot by the amendment to claim 1, which now recites "integers of 1 or more".

Item 14

The Examiner states that the biosensor system of claims 1-3 and 10 do not require any specific binding partner/pair to biosensor chip or to nanoparticle. As discussed above, with regard to item 11, X may be a functional moiety or a residue of one of the constituents forming the biological pair. Additionally, in Examples 3 and 4 of the specification, fine particles are directly bound to biosensor chip surface without the formation of biological specific binding pair. In these Examples, biotin is bound to fine particles. Then, specific bonding of streptavidin to biotin in the thus prepared biosensor system, as well as non-specific bonding of BSA to the biosensor system is observed. It is not necessary that the analyte is first bound to a specific binding partner. Therefore, this portion of the rejection is improper and should be withdrawn.

Item 15

The Examiner states that the linkage of "L" to "PCL" and "W^1" are not clear with respect to claim 4. Specifically, the Examiner states that "L" in formula (I) is a bivalent linkage, but the groups in claim 4 are disclosed as terminal groups (one open linkage), and therefore, it is unclear how these groups are linked to PCL and W^1.

Page 9, lines 18-22 of Applicants' specification teaches that L stands for a linkage to said particle surface, via a group or moiety which is capable of linking to said surface (e.g., by chemical binding or chemical adsorption, or covalent bonding via surface –OH

group formed by hydroxylation where the particle is made of metal oxide.) Therefore, this portion of the rejection is improper and should be withdrawn.

Item 16

The rejection of claims 12-15 under 35 U.S.C. § 112, second paragraph as being incomplete for omitting essential steps is respectfully traversed.

The Examiner states that the omitted steps are: determination steps to determine the change in the extent of linkage i.e. the steps how the "change in the extent of linkage" is determined.

However, the claims do not need to include determination steps to determine the change in the extent of linkage, because the use of such steps in competitive assays are well known to those of ordinary skill in the art. Furthermore, the specification does not need to include what is well known and in common use by those skilled in the art. See Puget Sound Salmon Egg Comp., Inc. v. Shoshoni, Inc. 168 USPQ 154 (1970).

Therefore, this rejection is improper and should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The patentability of the present invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Item 18

The rejection of claims 1-11 under 35 U.S.C. § 103(a) as being unpatentable over Weiss et al. taken in combination with Barry et al. and Natan is respectfully traversed.

The Examiner states:

> "In the nanoparticle of formula (I) of the present invention, when W^2-PEG-W^1-L is same in $(X\text{-}W^2\text{-PEG-}W^1\text{-L})_x$ and $(Y\text{-}W^2\text{-PEG-}W^1\text{-L})_y$, and when Y stands for functional moiety X, the polyethylene glycol (PEG) modified nanoparticles can be viewed as a nanoparticle linked with a PEG linker in which the other end of the linker has a functional moiety capable of binding to biomolecular

targer [sic] (note that W^1 and W^2 can be a single bond and L stands for linker or linkage portion)."

The present invention relates to a biosensor system which comprises, as a set, nanoparticles and a biosensor chip wherein:

a) unlike the above-quoted acknowledgment of the Examiner, X and Y are different from each other in $(X\text{-}W^2\text{-PEG-}W^1\text{-L})_x$ and $(Y\text{-}W^2\text{-PEG-}W^1\text{-L})_y$ of the nanoparticles of formula (I),

b) "X stands for a functional group or a functional moiety capable of binding directly to a biosensor chip surface" and

c) said biosensor system comprises, as a set, said nanoparticles and a biosensor chip having a surface to which the nanoparticles can be bound via X and which surface is made of glass or a material corresponding to that of PLC (hereinafter referred to as "the biosensor chip").

Owing to the above-mentioned features a), b) and c), the present invention provides a biosensor system as mentioned in Example 3 of Applicants' specification.

Said system comprises a biosensor chip having a modified surface which is like the one illustrated in Fig. 1, a). Although this biosensor chip has PEG-modified nanoparticles on its surface, it is capable of detecting analyte with a remarkably high sensitivity as compared with a biosensor chip which supports no such nanoparticles on its surface, when used for SPR (surface plasmon resonance). For a better understanding of this effect, please see the data of Example 2 of the present specification.

Such action and effects of the present invention (hereinafter referred to as "the effect of the present invention") could not have been foreseen from any combination of the references cited by the Examiner.

Weiss et al. disclose semiconductor nanoparticles linked to an affinity molecule through a linking agent. The linking agent comprises two linking portions (functional moieties).

As admitted by the Examiner, Weiss et al. fail to disclose PEG linker to link nanoparticles to the biomolecular target.

Barry et al. disclose nanoparticles linked to biomolecular target via a linker molecule. Furthermore, it is mentioned in Barry et al. that the linker can be bifunctional PEG linker terminated with same or different reactive functional moieties.

Attention should be paid, however, to the fact that the nanoparticles of Barry et al. are a so-called polymer micelle which is assembled by self-agglutination of hydrophobic/hydrophilic (PEG) block copolymer in an aqueous solution. Further, Barry et al. fail to teach or suggest the idea of using a block copolymer having plural kinds of hydrophilic PEG segments.

One of ordinary skill in the art would not have foreseen that a linker which contains such hydrophilic PEG segments in a polymer molecule would be able to be successfully used for the surface modification of semiconductor nanocrystal.

Thus, the use of two linkers: $(X\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_x$ and $(Y\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_y$, is not suggested even by a combination of Weiss et al. and Barry et al.

The Examiner further states:

> "Natan et al. disclose biosensor chip (glass, metal etc.) containing binding partner... coupled to nanoparticle... and detection of analyte from the measurement of change in electrical resistance or surface plasmon resonance..."

As schematically illustrated in FIG. 1C of Natan, however, the binding partner is directly coupled to nanoparticle, independent of BSA. In other words, Natan suggests that it should be avoided to connect a binding partner to BSA on a BSA-coated nanoparticle. The reason may be that, since Natan aims at the direction of analyte from the measurement of change in electrical resistance or surface plasmon resonance, consideration was taken so that the distance between biosensor chip and nanoparticle might not increase.

Hence, it would be natural to think that, even though a skilled person had conceived an idea of using PEG, they would not have considered connecting a binding partner to nanoparticle via PEG, but would have tried to adhere PEG, instead of BSA, to that area of nanoparticle where there existed no binding partner.

Therefore, even if Weiss et al. and Barry et al. are combined with Natan, it would not have motivated one of ordinary skill in the art to form nanoparticles with use of two linkers: $(X\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_x$ and $(Y\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_y$.

For these reasons, the invention of claims 1-11 is clearly patentable over Weiss et al. taken in combination with Barry et al. and Natan.

Item 19

The rejection of claims 1-15 under 35 U.S.C. § 103(a) as being unpatentable over Ewart et al. in view of Kataoka et al. and Barry et al. is respectfully traversed.

Ewart et al. does not teach or suggest forming nanoparticles with the use of the above-mentioned two linkers: $(X\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_x$ and $(Y\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_y$.

Kataoka '2003, on the other hand, discloses an idea of modifying biosensor chip surface with a polymer (e.g. general formula (I) of Kataoka '2003 where m = 0) similar to $Y\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L$ as employed in the present invention. Kataoka '2003 further teaches that the use of thus surface-modified biosensor chip achieves SPR properties which are significantly superior to conventional arts. Hence, it is unthinkable that Kataoka '2003 suggests the necessity of using nanoparticle probe in combination.

The nanoparticles of Barry et al. are formed from hydrophobic/hydrophilic block copolymers as mentioned above, and, therefore, a combination of Barry et al. and Ewart et al. would have suggested neither an idea of connecting PEG segment-containing linker to the nanoparticle of Ewart et al., nor the use of nanoparticles which support the above-mentioned two linkers: $(X\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_x$ and $(Y\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_y$.

Thus, it is evident that Barry et al. and Ewart et al. fail to teach or suggest using nanoparticles which support the above-mentioned two linkers: $(X\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_x$ and $(Y\text{-}W^2\text{-}PEG\text{-}W^1\text{-}L)_y$. Hence, there would have been no motivation to use such nanoparticles in combination with biosensor chip of Kataoka '2003 as a set. Therefore, even if Ewart et al. and Barry et al. are combined with Kataoka '2003, there is no motivation to construct the biosensor system of the present invention which has the above-mentioned features a), b) and c). The combination of the references also fails to teach or suggest the effect of the present invention as achieved by said features.

For these reasons, the invention of claims 1-15 is clearly patentable over Ewart et al. in view of Kataoka et al. and Barry et al.

Item 20

The rejection of claims 1-15 under 35 U.S.C. § 103(a) as being unpatentable over Ewart et al. in view of Kataoka et al. is respectfully traversed.

As discussed above, Ewart et al. do not teach or suggest forming nanoparticles with the use of the above-mentioned two linkers.

Kataoka '2004 discloses a metal fine particle which supports Y-W^2-PEG-W^1-L as used in the present invention. Kataoka '2004, however, only conducts "cohesion test" between particles with use of the particles mentioned therein (see [0075] and [0076] of Kataoka '2004), and suggests no idea of using such particles with biosensor chip as a set.

Neither reference provides motivation to replace a nanoparticle which is used in the displacement competition assay of Ewart et al. with the metal fine particle of Kataoka '2004.

Further, the combination of references fails to teach or suggest the effects of the present invention would be achieved.

For these reasons, the invention of claims 1-15 is clearly patentable over Ewart et al. in view of Kataoka et al.

Double Patenting Rejections

Item 22

The provisional rejection of claims 1-15 under obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/507, 303 in view of Ewart et al. and Barry et al. is respectfully traversed.

The claims of copending application '303 are directed to a biosensor surface and a method for preparing the surface. The claims do not disclose a biosensor system comprising nanoparticles and a biosensor chip, as in the Applicants' claims.

Application '303 teaches that, by increasing the density of PEG on the surface of PEG-modified biosensor chip of Kataoka '2003, it is possible to markedly reduce the

non-specific adsorption of uninteresting protein or the link onto the surface of biosensor chip, as compared with Kataoka '2003.

As admitted by the Examiner, application '303 fails to teach the polymer on a nanoparticle or in a nanoparticle based on biosensor selection system.

Application '303 would not have motivated one of ordinary skill in the art to use a biosensor chip with various kinds of nanoparticles as a set. Nor would it have been possible for one of ordinary skill in the art to foresee that such a method of modifying the surface of biosensor chip would be able to be successfully applicable to known nanoparticles.

For these reasons, the invention of claims 1-15 is clearly patentable over the claims 1-13 of copending application '303 in view of Ewart et al. and Barry et al.

Item 23

The provisional rejection of claims 1-15 under obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/275,904 in view of Ewart et al. and Barry et al. is respectfully traversed.

Copending application 10/275,904 is published as U.S. Patent Application Publication 2003/0171506, as discussed above in item 19. The claims of application '904 are directed to a polymer composition and a method for making biosensor chips using the polymer. The claims do not disclose a biosensor system comprising nanoparticles and a biosensor chip, as in Applicants' claims. Furthermore, the arguments set forth regarding Item 19 are also applicable to this rejection.

For these reasons, the invention of claims 1-15 is clearly patentable over the claims 1-8 of copending Application No. 10/275,904 in view of Ewart et al. and Barry et al.

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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